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DRUGS CONTAINING PHOSPHOAMINES IN COMBINATION WITH AN ALKYL GLYCEROL

[No inventor given]

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DRUGS CONTAINING PHOSPHOAMINES IN COMBINATION WITH AN ALKYL GLYCEROL

[Arneimittel, welche alkylphosphoamine in kombination mit einem alkylglycerin enthalten]

Applicant: Max Planck Society for the Promotion of Sciences, Registered Association

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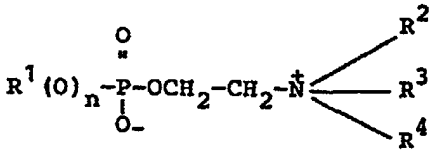
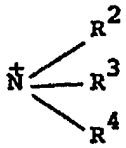
Description

EP-A1 108 565 concerns compounds of the following formula:



wherein R^1 is an aliphatic C_8-C_{30} hydrocarbon residue, and R^2, R^3, and R^4 denote hydrogen or lower alkyl residues, or the following group:



[or they] denote a cyclic ammonium residue, and n = 0 or 1. For these compounds, it is indicated that they inhibit the propagation of tumor cells and prolong the lifetime of warm-blooded animals which have tumors; furthermore, an antifungal effect is mentioned.

The invention concerns drugs which are particularly suitable for the treatment of tumors.

The drugs in accordance with the invention and Claim 1 have, for example, an improved effect, in comparison to the agents which are known from EP-A1 108 565.

It is known that up to now, there has been no drug available for the treatment of tumors–particularly for malignant tumors–which is satisfactory in any respect. Thus, for example, for the topical treatment of skin metastases with patients with metastasizing tumors, only 5-fluorouracil is available at present. Refinements of other cytostatic drugs have not been followed up to clinical readiness for this type of application. On the other hand, from a clinical

perspective, such a concept is particularly desirable in a palliative therapy approach, since alternative treatment concepts, such as surgical measures, radiation therapy, and systemic chemotherapy represent comparatively aggressive therapy modalities. Furthermore, a considerable number of patients are available as potential treatment candidates for such a topical treatment. Thus, for example, the fraction of patients with carcinoma of the breast, having a skin involvement is approximately 25 to 35%.

The prerequisites for topical treatment with regard to the active substance to be used are compatibility with the skin, cytoxic effectiveness with respect to tumor cells, and sufficient deep penetration.

The goal of the invention is therefore primarily to create a drug suitable for the topical treatment of tumors. Another goal of the invention is to create a drug which is generally applicable in other application forms also and which combines a good effectiveness against tumors with a low toxicity and can therefore be generally used in tumor therapy.

These goals are attained, in accordance with the invention, by a drug that is characterized in that it contains, as an active substance, at least one compound of general formula I or I', in accordance with Claims 1 and 8:

$$R - Y - PO_2^{\ominus} - X - R_1$$

or a physiologically acceptable salt hereof, optionally together with the usual pharmacological additives and diluents. Preferably, the following can be taken into consideration as active

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* [Numbers in the margin indicate pagination in the foreign text.]

substances: hexadecyl phosphocholine, oleyl phosphocholine, hexadecyl phosphoric acid-(N,N)-bis-(2-chloroethyl)amide.

Formulas I and I' also comprise the possible enantiomers and diasteromers. If the compounds are racemates, then they can be split into optically active isomers in a known manner, for example, by means of an optically active acid. Preferably, however, enantiomers or optionally, diastereomer starting substances are used from the very beginning, wherein as an end product, a correspondingly pure optically active or diastereomer compounds are obtained.

Within the framework of the invention, R is preferably an alkyl group of the indicated chain length, which is linked with the oxygen of the glycol residue via a terminal C atom or also a C atom within the alkyl chain (for example, via the C-2 atom 2 or C-3 atom, or another middle C atom). This alkyl chain can be straight or branched. The alkyl chain R can contain two or three carbon double bonds or triple bonds, which can also be present mixed.

In addition to the saturated, straight-chain alkyl residues, there are preferably those with one or two carbon double bonds in the molecule. Particularly preferred are those substituents R, which contain an alkyl residue with 14 to 20, preferably 15 to 20, in particular, 16 to 20 C atoms or a corresponding alkyl residue with 14 to 20, preferably 15 to 20, especially 16 to 20 C atoms.

Examples of unsaturated residues R are the following: 9-octadecenyl residue (oleyl alcohol residue; in particular, R denotes this 9-octadecenyl residue in the formula I or I'), 15-hexadecenyl residue, 9,12-octadecadienyl residue (linoleyl residue).

If more than one double or triple bond is present, they are conjugated. Examples of saturated and unsubstituted residues R are the following: tetradecyl residue, hexadecyl residue, octadecyl residue.

If R_1 or R_2 denotes an unsubstituted alkyl group, then it consists of, for example, 1-6 atoms, preferably 1-4 C atoms.

If R_1 or R_2 are substituted, then we are dealing with, in particular, straight-chain alkyl residues; in this case, R_1 preferably consists of 2-6 C atoms, wherein the indicated substituents preferably stand in the ω position of the alkyl or alkenyl group R_1 or R_2; for example, we are dealing with the ethyl or straight propyl residue with one of the indicated substitutents in the ω position (this means in the 2 position with ethyl and in the 3 position with propyl).

Among the substituents of R_1, the trialkylammonium ethyl residues are preferred if X is an oxygen atom, wherein the trialkyl residues preferably consist of one, two, or three C atoms; preferably we are dealing with methyl groups. The trimethylammonium ethyl residue is therefore particularly preferred. In this particularly preferred embodiment, the compounds of formula I are phosphatidyl choline derivatives.

The active substances according to Product Claim 8 are new compounds. Of these new compounds, the following can be preferably taken into consideration as active substances in accordance with the invention:

oleylpospho-(N,N,N-trimethyl)propanolamine,

oleylpospho-(N,N,N-trimethyl)butanolamine,

oleylpospho-(N,N,N-trimethyl)pentanolamine,

oleylphosphoserine,

oleylphosphoethanolamine,

oleylphosphopropanolamine,

oleylphosphobutanolamine,

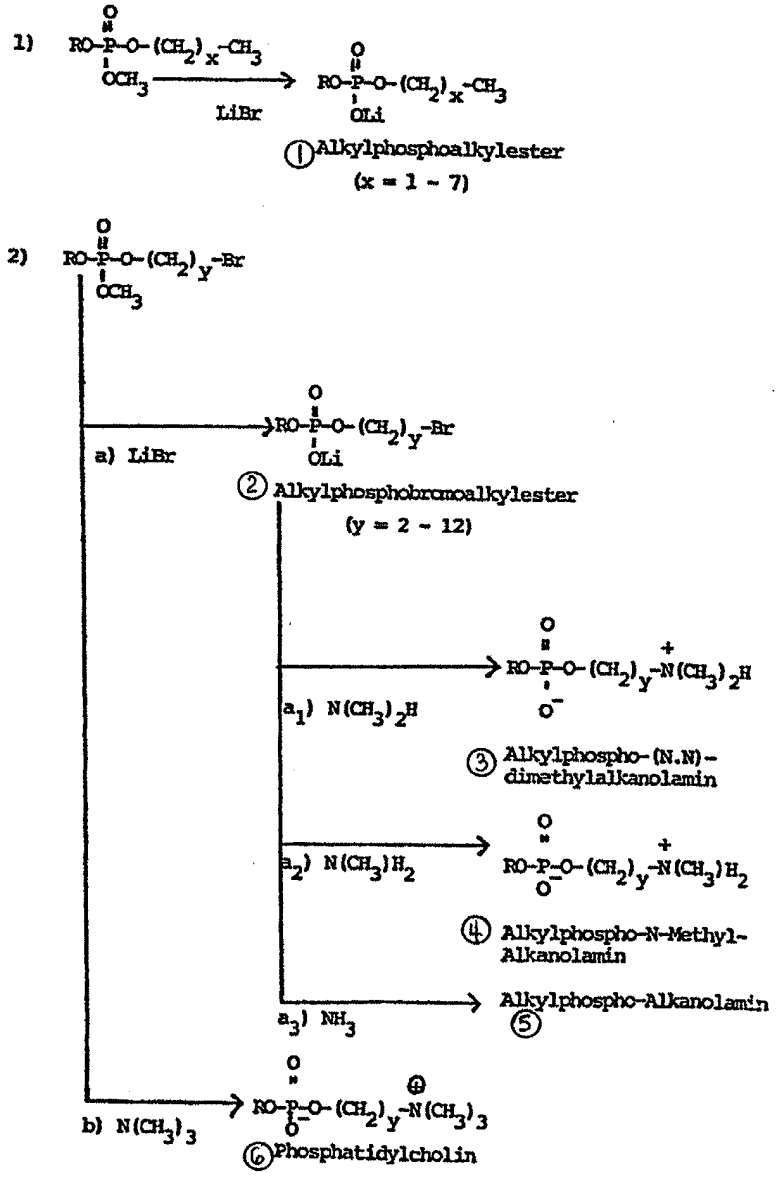
oleylphosphoglycerol,

hexadecylpospho-(N,N,N-trimethyl)propanolamine.

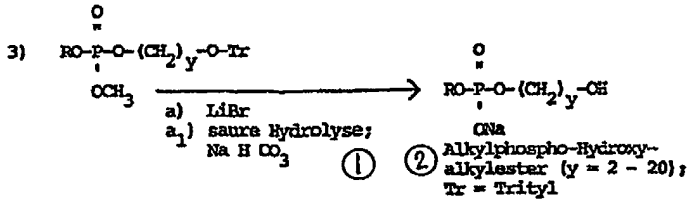
Inner salts (for example, when R_1 denotes a trimethylammonium alkyl group) or salts with physiologically acceptable cations can be taken into consideration as salts. The drugs in accordance with the invention or compounds can be present as inner salts, for example, if R_1 contains an amino group. If inner salts are not present or the residue R_1 does not contain a basic group, the negative charge of the phosphoric acid group is saturated by a physiologically acceptable cation. The following, for example, can be taken into consideration as such physiologically acceptable cations: alkali cations (Na, K), alkaline-earth cations (Mg, Ca), or the cations of organic amines, such as guanidinium, morpholinium, cyclohexylammonium cation, ethylenediammonium cation, piperazonium cation (in the two latter cases, monobasic or dibasic) or the cation derived from an amine of the formula $NR_aR_bR_c$, wherein the residues R_a to R_c are the same or different, and denote hydrogen, C_1-C_2 alkyl groups or oxyethylene groups. If they are cations, derived from an amine of the formula $R_aR_bR_c$, then we are preferably dealing with the ammonium cation or an ammonium cation substituted with one to three C_1-C_2 alkyl groups or an ammonium cation substituted with one to three 2-hydroxyethyl groups.

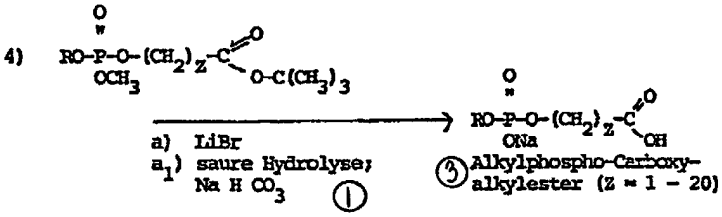
Production of the active substances according to general formula I or I' can take place according to methods which are, in fact, known. The basic structure can be easily obtained by reacting a compound of the formula ROH or a functional derivative thereof with phosphoroxychloride and triethylamine, reacting the product with a compound HXR_1, and acidic cleavage, wherein R, R_1, and X have the aforementioned meanings.

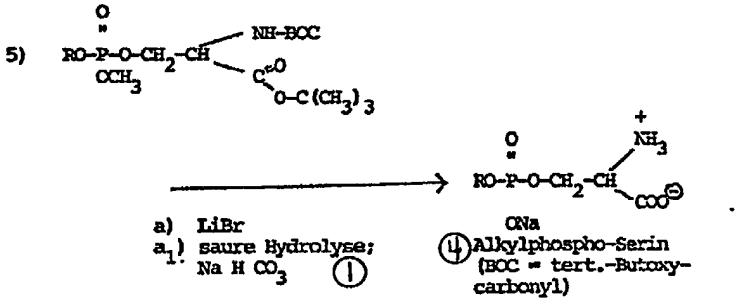
The production method for the compounds of formulas I and I' is explained schematically, by way of example, in the following reaction equations: (The group OCH_3 in the corresponding formulas are representative of the group OZ.)

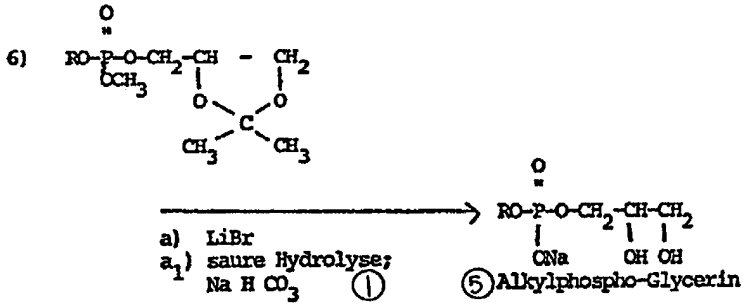


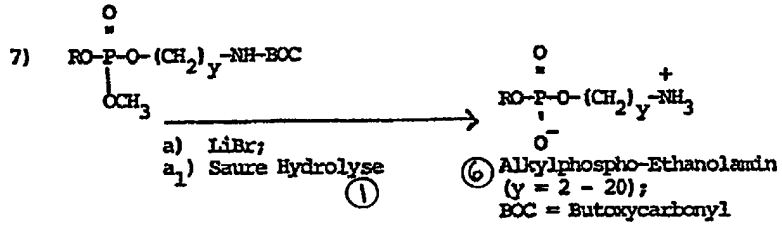
Key:
1 Alkylphosphoalkyl ester
2 Alkylphosphobromoalkyl ester
3 Alkylphospho-(N.N)-dimethylalkanolamine
4 Alkylphospho-N-methylalkanolamine
5 Alkylphosphoalkanolamine
6 Phosphatidyl choline

3) 
RO-P-O-(CH2)y-O-Tr
OCH3
a) LiBr
a1) saure Hydrolyse;
Na H CO3
1
RO-P-O-(CH2)y-OH
ONa
2 Alkylphospho-Hydroxy-alkylester (y = 2 - 20);
Tr = Trityl

4) 
RO-P-O-(CH2)z-C
O-C(CH3)3
OCH3
a) LiBr
a1) saure Hydrolyse;
Na H CO3
1
RO-P-O-(CH2)z-C
ONa
OH
3 Alkylphospho-Carboxy-alkylester (Z = 1 - 20)

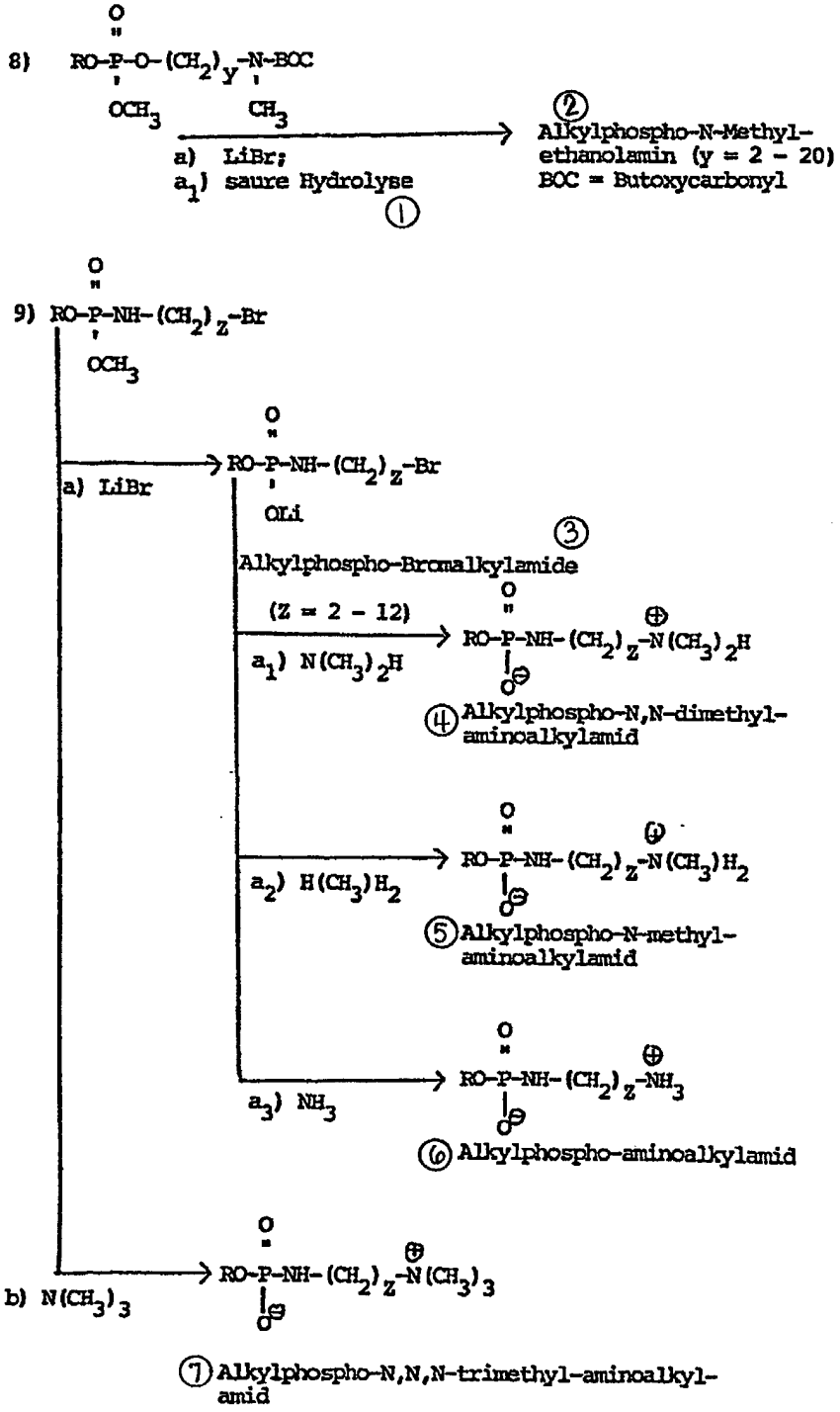
5) 
RO-P-O-CH2-CH
NH-BOC
C
O-C(CH3)3
OCH3
a) LiBr
a1) saure Hydrolyse;
Na H CO3
1
RO-P-O-CH2-CH
NH3+
COO⊖
ONa
4 Alkylphospho-Serin
(BOC = tert.-Butoxy-carbonyl)

6) 
RO-P-O-CH2-CH - CH2
OCH3
O
C
O
CH3
CH3
a) LiBr
a1) saure Hydrolyse;
Na H CO3
1
RO-P-O-CH2-CH-CH2
ONa
OH OH
5 Alkylphospho-Glycerin

7) 
RO-P-O-(CH2)y-NH-BOC
OCH3
a) LiBr;
a1) Saure Hydrolyse
1
RO-P-O-(CH2)y-NH3+
O⊖
6 Alkylphospho-Ethanolamin
(y = 2 - 20);
BOC = Butoxycarbonyl

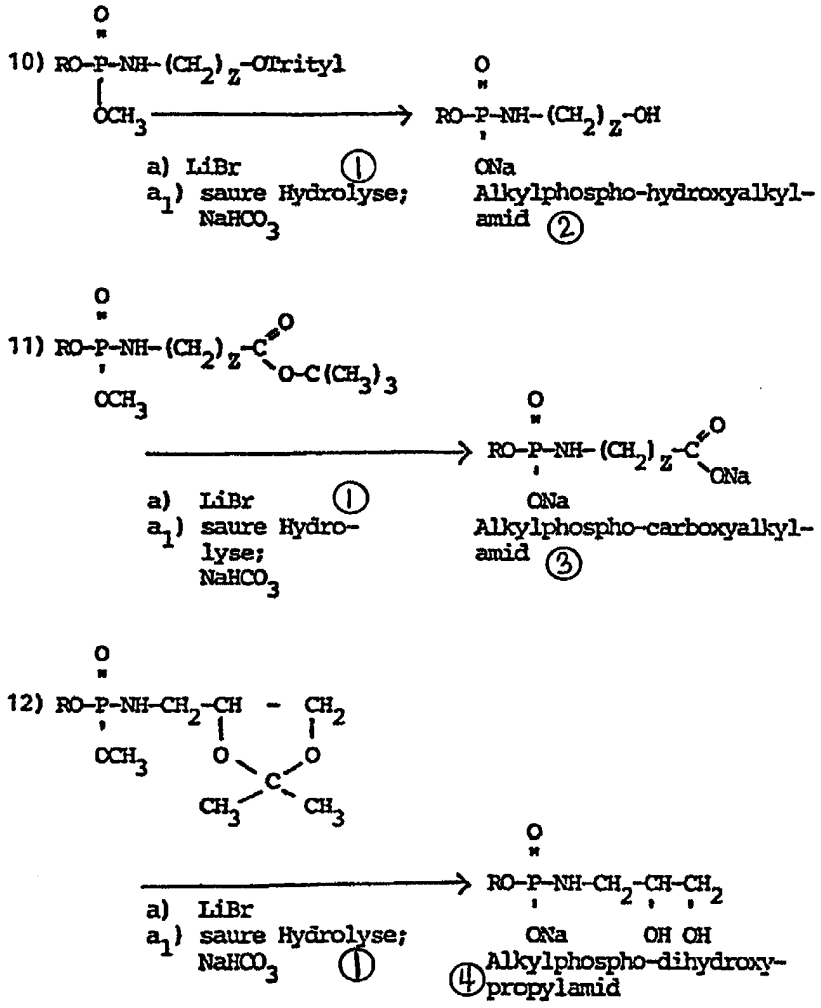
[Key to page 5:]

1 Acidic hydrolysis
2 Alkylphosphohydroxyalkyl ester
3 Alkylphosphocarboxyalkyl ester
4 Alkylphosphoserine
5 Alkylphosphoglycerol
6 Alkylphosphoethanolamine


8) RO-P(O)(OCH3)-O-(CH2)y-N-BOC
CH3
a) LiBr;
a1) saure Hydrolyse
①
②
Alkylphospho-N-Methyl-ethanolamin (y = 2 - 20)
BOC = Butoxycarbonyl
9) RO-P(O)(OCH3)-NH-(CH2)z-Br
a) LiBr
RO-P(O)(OLi)-NH-(CH2)z-Br
③
Alkylphospho-Bromalkylamide
(Z = 2 - 12)
a1) N(CH3)2H
RO-P(O)(O⊖)-NH-(CH2)z-N⊕(CH3)2H
④ Alkylphospho-N,N-dimethyl-aminoalkylamid
a2) H(CH3)H2
RO-P(O)(O⊖)-NH-(CH2)z-N⊕(CH3)H2
⑤ Alkylphospho-N-methyl-aminoalkylamid
a3) NH3
RO-P(O)(O⊖)-NH-(CH2)z-N⊕H3
⑥ Alkylphospho-aminoalkylamid
b) N(CH3)3
RO-P(O)(O⊖)-NH-(CH2)z-N⊕(CH3)3
⑦ Alkylphospho-N,N,N-trimethyl-aminoalkyl-amid

[Key to page 6:]

1 Acid hydrolysis
2 Alkylphospho-N-methylethanolamine
3 Alkylphosphobromoalkylamide
4 Alkylphospho-N,N-dimethylaminoalkylamide
5 Alkylphospho-N-methylaminoalkylamide
6 Alkylphosphoaminoalkylamide
7 Alkylphospho-N,N,N-trimethylaminoalkylamide



Key:
1 Acidic hydrolysis
2 Alkylphosphohydroxyalkylamide
3 Alkylphosphocarboxyalkylamide
4 Alkylphosphodihydroxypropylamide

Additional information regarding the method of the invention:

In the starting substances of formula III, any hydroxy groups, carboxy groups, amino groups, or C_1-C_6 alkylamino groups, present in the residue R^1 or in the residue R^2 also (if X is the group NR^2), can be protected by the usual protecting groups. Adjacent hydroxy groups can be protected by ketalization with an aliphatically saturated C_3-C_6 ketone.

We are hereby dealing with residues, that can be readily split off by hydrolysis or hydrogenolysis and are split off during or after the reaction. If such protecting groups are not split off during the process reaction, then a splitting off after the reaction takes place. Frequently, the starting compounds already contain such protecting groups as a result of their production.

These protecting groups are, for example, acyl groups that can be easily split off solvolytically or groups which can be split off by means of hydrogenation. The protecting groups that can be split off solvolytically are, for example, split off by saponification with dilute acids (for example, acetic acid, perchloric acid, hydrochloric acid, sulfuric acid, formic acid, trifluoroacetic acid) or by means of basic substances (potash, soda, aqueous alkali solution, alcoholic alkali solutions, NH_3) at temperatures between -50 and 150°C, in particular, between 0 and 100°C. Groups that can be split off by means of hydrogenation, such as arylalkyl residues (benzyl residue) or hydroxycarbonyl residues (carbobenzoxy residue), are appropriately split off by catalytic hydrogenation in the presence of the usual hydrogenation catalysts (noble metal catalysts), in particular, palladium catalysts or also platinum catalysts (platinum oxide), Raney nickel, in a solvent or suspension agent, optionally under increased pressure (for example, 1-50 bar) at temperatures between 20-150°C, especially 30-100°C, preferably 40-80°C. As solvents or suspension agents for the splitting off of such protecting groups, one can take into consideration, for example, the following: water, lower aliphatic alcohols, cyclic ethers, such as dioxane or tetrahydrofuran, aliphatic ethers, halogenated hydrocarbons, dimethylformamide and so forth, and mixtures of these agents. As protecting groups that can be split off by hydrogenolysis, one can take into consideration, for example: benzyl residue, α-phenylethyl residue, benzyl residues substituted on the benzene core (p-bromo- or p-nitrobenzyl residue), carbobenzoxy residue, carbobenzothio residue, tert-butoxycarbonyl residue. Examples of hydrolytically splittable

residues are the following: trifluoroacetyl residue, phthalyl residue, trityl residue, p-toluenesulfonyl residue, tert-butoxycarbonyl residue, tert-butyl residue, dimethyl methylene residue, and the like, and lower alkanoyl residues, such as acetyl residue, formyl residue, tert-butylcarboxy residue and the like.

In particular, the protecting groups which are common in peptide synthesis and the splitting methods that are usual there can be taken into consideration. In this regard, reference is made to, among other publications, the book by Jesse P. Greenstein and Milton Winitz, Chemistry of Amino Acids, New York 1961, John Wiley and Sons, Inc., Volume 2–for example, page 883 and following. The carbalkoxy group (for example, low-molecular) can also be taken into consideration.

The splitting off of the group OZ (preferably, this is OCH_3) takes place, for example, with alkali bromides or alkali iodides, lower alkyl magnesium halides or with primary, secondary, or tertiary amines, in particular, the corresponding lower alkyl amines, such as tertiary C_1-C_6 alkyl amines (trimethylamine). As lower alkyl magnesium halides, one can take into consideration, for example, the following: methyl magnesium iodide, methyl magnesium bromide (in this case, the solvents are lower aliphatic ethers, such as diethyl ether).

The splitting off of the group OZ from a compound of formula III takes place at temperatures between 10 and 150°C, preferably 10 and 80°C, especially 50 and 80°C, wherein the reaction product obtained up to then is dissolved in an inert agent after removal of the solvents. The following can be taken into consideration as such inert agents: saturated aliphatic C_3-C_8 ketones (ethyl methyl ketone, diethyl ketone, acetone), cyclic ethers, acyclic lower aliphatic ethers (for example, diethyl ether). Generally, 1.5 to 3 mol of the aforementioned splitting agents, preferably 2 mol, are used per mole of the used compound III.

The reaction of obtained products (for example, compounds in which R^1 and/or R^2 denote haloalkyl) with ammonia or an amine of the formula $NR^3R^4R^5$ takes place at temperatures between 10 and 200°C, preferably 20 and 150°C, especially 40 and 80°C, with or without solvents. If a solvent or suspension agent is used, the following can be taken into consideration for this: aromatic hydrocarbons, such as pentane, hexane, heptane, benzene, mesitylene, toluene, xylene; lower aliphatic ketones, such as acetone, methyl ethyl ketone; halogenated hydrocarbons, such as chloroform, trichloroethylene, carbon tetrachloride, chlorobenzene, methylene chloride; cyclic ethers, such as tetrahydrofuran and dioxane; lower aliphatic acyclic ethers (diethyl ether, diisopropyl ether); lower aliphatic alcohols (1-6 C atoms), such as methanol, ethanol, isopropanol, amyl alcohol, butanol, tert-butanol; amides and N-alkyl-substituted amides of aliphatic C_1-C_4 carboxylic acids (dimethylformamide, dimethylacetamide); C_1-C_6 dialkyl sulfones (dimethylsulfone, tetramethylsulfone); C_1-C_6 dialkyl sulfoxides (dimethyl sulfoxide), and other aprotic agents, such as N-methylpyrrolidone, tetramethylurea, hexamethylphosphoric acid triamide, acetonitrile. The individual alkyl residues of the aforementioned solvents contain, for example, 1-6, in particular, 1-4 carbon atoms. Also, mixtures of these agents and mixtures with water can be taken into consideration as the reaction medium. The reaction is carried out, for example, at temperatures of 0 to 200°C, preferably, 20 to 150°C, or also 50 to 120°C. If a solvent or dispersant is used, the work is frequently carried out at the reflux temperature of this agent.

This aminization reaction is appropriately carried out in the presence of basic substances. For example, the following can be taken into consideration as basic substances: alkali hydroxides, alkali carbonates, tertiary amines.

The alkylation of free amino groups in the residues R^1 and/or R^2 takes place at temperatures between 0 and 200°C, preferably between 20 and 150°C, in particular, 20 and 80°C.

This alkylation takes place, for example, by reacting compounds with the formula R'Hal, $ArSO_2OR'$, and $SO_2(OR'_3)_2$, wherein Hal is a halogen atom (especially, chlorine, bromine, or iodine) and AR an aromatic residue (for example, a phenyl or naphthyl residue, substituted optionally with one or more lower alkyl residue and R' is a C_1-C_6 alkyl group. Examples are p-toluenesulfonate and C_1-C_6 alkyl esters, C_1-C_6 dialkyl sulfates and C_4-C_6 alkyl halides. The alkylation reaction is optionally carried out with the addition of the usual acid-binding agents, such as alkali hydroxides, alkali carbonates, alkali hydrogen carbonates, alkaline-earth carbonates, alkali acetates, tertiary amines (for example, trialkylamine, such as triethylamine), pyridine, or also alkali hydrides in inert solvents or suspension agents. As solvents or dispersants, one can take, for example, the following into consideration: aromatic hydrocarbons, such as benzene, toluene, xylene; aliphatic ketones, such as acetone, methyl ethyl ketone; halogenated hydrocarbons, such as chloroform, carbon tetrachloride, chlorobenzene, methylene chloride; aliphatic ethers, such as butyl ether, cyclic ethers, such as tetrahydrofuran, dioxane; sulfoxide, such as dimethyl sulfoxide; tertiary acid amides, such as dimethylformamide, N-methylpyrrolidone, hexamethylphosphoric acid triamide; aliphatic alcohols, such as methanol, ethanol, isopropanol, amyl alcohol, tert-butanol, cycloaliphatic hydrocarbons, such as cyclohexane and the like. Also aqueous mixtures of the aforementioned solvents can be used. Frequently, the work is carried out at the reflux temperature of the used solvents or dispersants. Frequently, the alkylation reaction components are used in excess. The alkylation can also be undertaken in the presence of tetraalkylammonium salts (especially, the halides) in combination with alkali hydroxides at temperatures between 0-100°C, preferably, 20-80°C in an aprotic solvent or also in chloroform or methylene chloride. As aprotic solvents, one can take into consideration, in particular, the following: tertiary amides (dimethylformamide,

N-methylpyrrolidone, hexamethylphosphoric triamide), dimethyl sulfoxide, acetonitrile, dimethoxyethane, acetone, tetrahydrofuran.

Those [sic] contained in the drug in accordance with the invention as active substances of the general formula I or I', are partially novel and insofar, an object of the invention also. They have a pronounced cytotoxic effectiveness, which was demonstrated both in vivo, on chemically induced carcinoma of the breast in rats, and also in vitro, on leukemia cells in cell culture. Moreover, in a clinical pilot study with female patients with carcinoma of the breast, skin metastases were completely healed with topical use.

The following compounds and their physiologically acceptable salts are novel:

Compounds of the following general formula:

I'

wherein R denotes a saturated or unsaturated hydrocarbon residue with 12 to 24 C atoms, which can also be halogen-substituted; X is an oxygen atom; NH or NR_2; and Y, an oxygen atom or NH; the residue R_1

a) represents a C_1-C_8 alkyl group, an unsaturated C_3-C_8 alkyl group, or an optionally unsaturated C_3-C_8 alkyl group, which is substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy, carboxy, C_3-C_8-cycloalkyl, or phenyl; or

b) represents a C_2 alkyl group, which is substituted with halogen, hydroxy, carboxy, C_3-C_8-cycloaklyl, or phenyl; or

c) represents an unsaturated C_2 alkyl group, which is substituted with di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, carboxy, C_3-C_8-cycloalkyl, or phenyl; or

d) represents a C_2 alkyl group, which is substituted with amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or tri-C_1-C_6 alkylamino, if X denotes oxygen, NH or NR_2, and Y represents the group NH, or if X denotes the group NH or NR_2, and Y represents oxygen; and R has the indicated meanings; or

e) it can mean 2-tert-butoxycarbonylaminoethyl, 2-tert-butoxycarbonylethyl, 2,3-isopropylidene dioxypropyl-(1), 2,3-dibenzyloxypropyl-(1), 1,3-dibenzyloxypropyl-(2), or N-C_1-C_6 alkylamino-C_2-C_6 alkyl, if X is an oxygen atom, and Y and R have the indicated meanings; or

f) it can mean 2,3-dihydroxypropyl-(1), if X is the NH group; and Y and R, have the indicated meanings;

and R_2 represents a 2,3 -dihydroxypropyl-(1) group, a C_1-C_8 alkyl group, or a C_2-C_8 alkyl group, which is unsaturated and/or is substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy, carboxy, C_3-C_8-cycloalkyl, or phenyl, wherein such compounds are excepted where in formula I', X and Y are both oxygen; R_1 is a saturated or unsaturated C_1-C_8 alkyl residue, which can also be substituted with hydroxy, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, or tri-C_1-C_6 alkylamino; and R represents a saturated or unsaturated C_{12}-C_{24} alkyl residue.

Especially for topical application, but also for preparation as a drug for other types of application, it has proved to be particularly favorable to use the compounds of general formula I or I' together with at least one alkyl glycerol with 3 to 12 carbon atoms in the alkyl residue, which can be present in the form of an ether group, bound to one of the primary or secondary OH

groups of the glycerol. Such alkyl glycerols increase or improve the effect of the compounds of general formula I or I' synergistically. Alkyl glycerols with 3 to 9 C atoms are hereby preferably used alone or in a mixture.

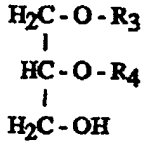
Particularly favorable effects, therefore, are produced by a synergistically acting drug, which contains

a) at least one compound of the following formula:

I

or a physiologically acceptable salt hereof, wherein in formula I, R denotes a saturated or unsaturated hydrocarbon residue with 12 to 24 C atoms, which can also be halogen-substituted; X represents an oxygen atom, NH, or NR_2; and Y is an oxygen atom or NH; R_1 is a C_1-C_8 alkyl group; or wherein R_1 represents a C_2-C_8 alkyl group, which is unsaturated and/or substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy, carboxy, C_3-C_8-cycloalkyl, or phenyl, and wherein R_1 can also mean 2-tert-butoxycarbonylaminoethyl, 2-tert-butoxycarbonylethyl, 2,3-isopropylidene dioxypropyl-(1), 2,3-dibenzyloxypropyl-(1), 1,3-dibenzyloxypropyl-(2) or N-C_1-C_6 alkylamino-C_2-C_6 alkyl, if X is an oxygen atom, and wherein R_1 can also mean 2,3-dihydroxypropyl-(1), if X is the NH group and R_2 represents a 2,3-dihydroxypropyl group, a C_1-C_8 alkyl group or a C_2-C_8 alkyl group, which is unsaturated and/or substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy, carboxy, C_3-C_8-cycloalkyl, or phenyl, and contains

b) an alkyl glycerol of the following general formula II:



in which one of the residues R_3 and R_4 denotes an alkyl group with 3 to 12 C atoms, and the other residue, an H atom, and optionally, other common pharmacological additives and diluents.

Such a mixture is designated below as a cascade also. The content of compound of general formula I or I' in mg/mL cascade is designated by an added index, in such a way that, for example, a cascade mixture, which contains 5 mg/mL compound of formula I or I', is designated as $cascade_5$; a mixture with 200 mg compound of formula I or I' per mL cascade is designated as $cascade_{200}$.

The production of the alkyl glycerols is known, for example, from DE-OS 33 43 530.8. For example, alkyl glycerol-water mixtures, which contain, for example, nonyl glycerol, octyl glycerol, hexyl glycerol, pentyl glycerol, propyl glycerol, and ethyl glycerol, are preferred. Preferably, such aqueous mixtures contain three of the aforementioned glycerol ethers–a lower (ethyl, propyl), an average (pentyl, hexyl), and a higher (nonyl, octyl), wherein the weight quantity of the lower ether is approximately as large as the sum of the weight quantities of the two other glycerol ethers. The water quantity is approximately equal to the quantity of the lower glycerol ether, and is, for example, half the total quantity of the glycerol ethers present. Examples of such glycerol ether-water mixtures are given below:

Water	Glycerolpropyl	Glycerolhexyl	Glycerolnonyl

		ether		ether		ether		
Parts by weight	2	:	2	:	1	:	1	
	Water	Glycerolethyl ether		Glycerolpentyl ether		Glycerloctyl ether		
Parts by weight	2	:	2	:	1	:	1	

The drug in accordance with the invention is particularly suitable for topical application. In order to treat skin tumors or skin metastases with this drug, the affected skin areas are rubbed, for example, with cascade$_5$ to cascade$_{200}$ twice to three times, daily. It has not been possible to observe harmful side effects, not even with patients who were treated over a period of 3 months. The remission of skin metastases is accompanied by a normalization of the skin, as it was possible to demonstrate clearly with tissue sections. Several female patients with skin metastases were treated in this manner, and a complete disappearance of the carcinoma of the breast-skin metastases was hereby observed.

The topical treatment with the preferred agent, in accordance with the invention and in the formulation cascade$_5$ to cascade$_{200}$, can also be used for the treatment of inner tumors or metastases by large-area rubbing of the skin. A therapeutically effective blood level is attained hereby via absorption through the skin. An advantage of this type of application is to be found in the fact that the preparations cascade$_5$ to cascade$_{200}$ are tolerated by the skin without any problems.

This preferred type of preparation of the drug in accordance with the invention and in the form of the solutions cascade$_5$ to cascade$_{200}$ is also very suitable for the production of

suppositories for rectal insertion. Inner tumors or inner metastases can also be treated well with it.

Another type of application of the drug in accordance with the invention consists in instillation in preformed body cavities. This type of application is particularly suitable for pleura carcinoses, malignant ascites, malignant pericardial effusions, and bladder carcinomas. In this case, the antitumor agents of general formula I, in accordance with the invention, are used either alone or in combination with the usual carrier agents and diluents, in particular also with cascades.

For systematic application, one can take into consideration oral or intravenous administration.

For oral administration, the compounds of general formula I are appropriately used in the form of a beverage. The following are suitable as carriers: milk, cocoa, fruit juice, or drinking water. The production of such drinking water can be done, for example, by diluting a concentrated alcoholic solution of a compound of formula I or I', in accordance with Claims 1 and/or 2, with water or another of the aforementioned agents. With rats, daily doses of 20, 40, and 60 mg/kg body weight, with the use of hexadecylphosphocholine and oleylphosphocholine, led to a complete remission of chemically induced carcinomas of the breast. These compounds proved to be more effective and more compatible than 1-octadecyl-2-methyl-rac-glycero-3-phosphocholine. The tumor model used for these experiments is a so-called hard model. This means that the findings made with this model can also be transferred to the human situation.

For intravenous administration via the intravenous infusion therapy, the compounds of formula I or I' are appropriately used in physiological saline solution. Other infusion solutions

can also be used hereby. The dosage in humans for such solutions is, for example, 1-10 mg/kg body weight.

Finally, several application types of the drug in accordance with the invention can be used combined, wherein the special topical compatibility leads to the skin being rubbed with one of the other application forms in a combined usage.

Another carrier mixture for the compounds of formula I or I', which has proved to be particularly good, consists of a mixture of approximately 4 parts by weight water, 4 parts by weight propyl glycerol and 2 parts by weight hexyl glycerol and nonyl glycerol.

The topical use of the drug in accordance with the invention in the particularly preferred preparation form cascade$_5$ to cascade$_{200}$ over a period of several months shows that the local toxicity is limited to an intensified flaking of the skin, similar to the local use of acetylsalicylic acid.

The invention thus makes available a new drug for the treatment of tumors and provides not only, in general, another antitumor agent, but rather brings, for the first time, an agent which is demonstrably effective with topical use in a clinical experiment. In this way, new possibilities are opened for the treatment of tumor patients.

For the production of corresponding drugs, at least one compound of formula I or I' is processed with common pharmaceutical carrier substances and/or diluents or other auxiliaries to form pharmaceutical preparations or are brought into a therapeutically applicable form. This takes place, for example, in that compounds of formula I or I', wherein the individual residues and symbols have the indicated meanings, or their physiologically acceptable salts, together with the usual carrier substances and/or diluents or auxiliaries are mixed or homogenized at

temperatures between 20 and 120°C, preferably, 30-100°; the mixture thus obtained for the production of preparations, which, in the dosage unit, contain 5 to 2000 mg, preferably 10 to 500 mg, in particular, 30 to 400 mg active substance of formula I or I', is poured into hollow cells of an appropriate size, or into capsules of the appropriate size, or granulated and then, optionally with the addition of other common auxiliaries, pressed into tablets. For example, compounds of formula I or I' are mixed with one or more of the following substances: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogen phosphate, highly disperse silica, talc, phenoxyethanol; the mixture obtained is granulated, optionally with an aqueous solution, which contains, as a component, at least gelatin, starch, polyvinylpyrrolidone, vinylpyrrolidone-vinyl acetate copolymer, and/or polyoxyethyl sorbitan monooleate; the granulate is homogenized, optionally with one or more of the aforementioned auxiliaries; and this mixture is pressed into tablets, or poured into capsules, wherein in the dosage unit, such tablets or capsules contain 5 to 2000 mg active substance of formula I or I'; or compounds of formula I or their salts are suspended and homogenized in melted hard fat at temperatures between 33-37°C after the addition of soya lecithin and optionally 0.1-0.5 part by weight phenoxyethanol (with reference to 1 part by weight compound I or I')'; and subsequently, the mixture is poured out into hollow cells, wherein the dosage unit contains 5 to 2000 mg active substance or optionally 0.1-0.5 part by weight phenoxyethanol (with reference to 1 part by weight compound I or I'); or compounds of formula I or I' or their salts are homogenized at a temperature between 50 to 120°C, preferably, 50 to 100°C, optionally in the presence of one or more emulsifiers and/or 0.1 -0.5 part by weight phenoxyethanol, with reference to 1 part by weight compound I or I', with at least one of the following substances: paraffin, Vaseline, aliphatic alcohol with 12 to 25 C atoms, aliphatic monocarboxylic acid with 15 to 20 C atoms, sorbitan

monopalmitate, polyoxyethylene polyol fatty acid ester; and the mixture obtained is emulsified with water, optionally with the addition of a multivalent lower aliphatic alcohol and/or phenoxyethanol between 50 and 120°C; or compounds of formula I or I' or their salts are dissolved in water or vegetable oil, optionally in the presence of 0.1-0.5 part by weight phenoxyethanol (with reference to 1 part by weight compound I or I') and optionally, in the presence of an emulsifier, at temperatures between 30-100°C; and optionally the solution thus obtained is filled with so much water or vegetable oil that the final solution contains 0.05 to 10 wt%, preferably 0.1 to 5 wt% active substance of formula I or formula I'.

The following, for example, can be taken into consideration as emulsifiers: nonionic emulsifiers and ionic emulsifiers. The nonionic emulsifiers are, for example, triglyceride mixtures of saturated vegetable fatty acids with C_8, C_{10}, and C_{12} or emulsifiers based on polyaddition products of ethylene oxide, such as alkyl- and acyl-substituted polyaddition products of ethylene oxide, polyethylene glycol fatty acid ester, reaction products of ethylene oxide with castor oil or hydrogenated castor oil, esters of hydrogenated castor oil fatty acids with oxyethylated glycerol. Furthermore, they may be emulsifiers based on fatty acid amides or fatty acid condensation products with hydrophilic groups. As ionic emulsifiers, one can take into consideration, for example, emulsifiers based on fatty acid monoesters of the glycerol or other multivalent alcohols (lunacera alba).

If in the production of the drugs, as indicated above, the active substance or substances of formula I or I' are used in the presence of a glycerol ether of formula II or a mixture of such glycerol ethers of formula II, a synergistic increase of the antitumor effect is observed. In this respect, the active substances of formula I or I' are used with 1 to 30, preferably 2 to 20 parts by weight (with reference to 1 part by weight of compound I or I') of at least one glycerol ether of

formula II or a mixture of such glycerol ethers or optionally 0.5-30, preferably 1-20 parts by weight water (likewise, relative to 1 part by weight of compound I or I'). This mixing with the glycerol ethers can take place during the production of the corresponding drugs at the beginning, but optionally also in a later production stage.

The compounds of formulas I and I', in accordance with the invention, show, for example, a good effect on rats with cancer of the mammary glands induced by 7,12-dimethylbenzanthracene; likewise, with carcinoma of the breast in rats induced by methylnitrosourea.

For example, a cessation of tumor growth in rats is attained with the aforementioned experimental method with a dosage of 10 mg/kg body weight; with higher dosages, a complete disappearance of the tumors is also attained.

The lowest effective dosage in the animal experiment indicated above is, for example:
5 mg/kg oral,
5 mg/kg intravenous.

As a general dosage range for the effect (animal experiment as above), the following, for example, can be taken into consideration:
50 mg/kg oral, especially 15-32 mg/kg;
5-50 mg/kg intravenous, especially 15-32 mg/kg.

The effect tendency of the compounds in accordance with the invention is comparable to the effect of the known drug active substance tamoxifen, but in this regard, there are, in particular, the following differences: the effect is stronger and of longer duration than the effect and duration of tamoxifen.

Indications for which the compounds in accordance with the invention can be taken into consideration: mammary gland cancer and other human types of cancer.

The pharmaceutical preparations generally contain between 5-2000 mg, for example, 10-400 mg of the active components in accordance with the invention.

The administration can be done, for example, in the form of tablets, capsules, pills, dragees, suppositories, ointments, gels, creams, powders, dusting powders, aerosols, or in liquid form. One can take the following into consideration, for example, as liquid forms of application: oily or alcoholic or aqueous solutions and suspensions and emulsions. Preferred forms of application are tablets which contain between 40 and 400 mg active substance or solutions which contain between 0.1% to 5% active substance.

The individual dosage of the active components in accordance with the invention can, for example, be the following:

a) with oral medicines, between 5-100 mg/kg body weight, preferably 15-50 mg/kg body weight;

b) with parenteral medicines (for example, intravenous, intramuscular), between 5-100 mg/kg body weight;

c) with medicines for local application on the skin and mucosa (for example, in the form of solutions, lotions, emulsions, ointments, and so on), between 50-2000 mg, preferably, 80-1500 mg.

-(In each case, the dosages are relative to the free base.)-

For example, the recommendation could be 3 times daily, 1 tablet with a content of 40-400 mg active substance or, for example, with an intravenous injection, 1-5 times daily, one

ampoule of 1-5 mL content with 50-250 mg substance. With oral administration, the minimum daily dosage is, for example, 120 mg; the maximum daily dosage, with oral administration, should not lie above 100 mg/kg body weight.

The acute toxicity of the compounds in accordance with the invention, with mice (expressed by the LD 50 mg/kg; method according to Miller and Tainter: Proc. Soc. Exper. Biol. a. Med. 57 (1944) 261) is, for example, between 200 and 450 mg/kg body weight with oral application.

The drugs can be used in human medicine, veterinary medicine, and in agriculture, alone or in a mixture with other pharmacologically active substances.

The invention is explained by the following examples.

Example 1

Hexadecylphosphoethanolamine

(Phosphorylation, ring closure and ring opening)

Hexadecanol (1 mol, 243 g) and triethylamine (1.8 mol, 180 g) are dissolved in 1.5 L THF (tetrahydrofuran) and added dropwise to a vigorously stirred solution of phosphoroxychloride (1.2 mol, 184 g) in 120 mL THF, in such a way that the temperature in the reaction vessel (three-neck, 5 L, with dropping funnel, thermometer, and stirrer) does not exceed 10°C. For the acceleration of the process, the reaction vessel is cooled with an ice-common salt mixture. Immediately after dropwise addition, the reaction is concluded (detection via TLC in ether: Rf values of 0.8 for the starting product [RF]; of 0.0 for the reaction product after hydrolysis with water).

The ice bath is removed, and a solution of ethanolamine (1.5 mol, 92 g) and triethylamine (1.8 mol, 180 g) in 1 L dioxane is dripped into the reaction mixture, while stirring vigorously, in such a way that the temperature in the reaction vessel rises to 65 to 70°C. Then, the ring formation is concluded (detection by TLC in ether: Rf value of 0.2). Filtration from the precipitated triethylamine hydrochloride, while still warm, is carried out and the filtrate is mixed with 1.5 L 2N formic acid, at 40 to 50°C. After 15 min, the ring opening is concluded (detection by TLC in ether: Rf value 0.0; TLC in chloroform/methanol/acetic acid/water 100:60:20:5 by volume: Rf value 0.8). Cooling to -20°C is undertaken, followed by filtration from the precipitate, which consists largely of pure hexadecylphosphoethanolamine. A chromatographic purification follows, in the case of slight impurities (see Example 2).

Microanalysis* (molecular weight 365.50):

(1) ber. (%):	C 59,15	H 11,03	N 3,83	P 8,48
(2) gef. (%):	59,01	10,95	3,79	8,31

Key: 1 Calculated (%):

2 Found (%):

* [Editor's note: In the microanalysis data and tables, commas in numbers represent decimal points.]

Example 2

Hexadecylphosphocholine monohydrate

(Methylation of 1)

The crystals obtained according to Example 1 are taken up, without further purification, in 1.2 L 2-propanol and 0.4 L dichloromethane. The suspension of the crystals is mixed, while stirring vigorously, with potassium carbonate (4 mol, 560 g) in 1 L water. The two-phase reaction mixture is mixed with dimethyl sulfate (4 mol, 500 g), in drops and while stirring, so that the temperature does not exceed 40°C. The reaction is ended 60 min after the dropwise addition (detection by TLC in chloroform/methanol/25% ammonia 50:50:5 by volume: Rf value 0.3). After phase separation at 20°C, the upper phase contains the product. The solvent is removed on a rotary evaporator, under vacuum, and the viscous residue is chromatographed on silica gel (Merck item 7733, silica gel 60, particle size 0.2 to 0.5 mm).

Chromatography

Silica gel, 2 kg, is mixed with chloroform/methanol/25% ammonia (200/15/1 by volume) and poured into a chromatography column. The viscous oil is dissolved in 800 mL of the aforementioned solvent mixture, and the crude product is added to the column (insoluble fractions are previously filtered off). Elution with flow agents of increasing polarity is carried out until the impurities are washed out. The product is finally eluted with chloroform/methanol/25% ammonia (50/50/5 by volume). The combined eluates are evaporated on a rotary evaporator, and the remaining water is removed with toluene. The residue is taken up in 600 mL dichloromethane

and mixed with 4 L acetone. The crystals deposited at -20°C are washed with cold acetone; then with pentane; and dried in a vacuum. The yield of pure hexadecylphosphocholine is 250 g (approx. 70%, relative to hexadecyl glycerol).

Microanalysis (molecular weight 407.58):

① ber. (%):	C 59,27	H 11,37	N 3,29	P 7,28
② gef. (%):	58,98	11,31	3,21	7,11

Key: 1 Calculated (%)

2 Found (%)

Example 3

2-Hexadecylphosphoethanolamine

(Phosphorylation, ring closure, ring opening)

The batch is prepared as described under Example 1, but for 0.1 mol. In order to attain good yields, the phosphorylation conditions must be modified somewhat–that is, the temperature in the phosphorylation step is increased to 25°C. Otherwise, the procedure and workup are as described.

Microanalysis (molecular weight 365.50)

(1) ber. (%):	C	59,15	H	11,03	N	3,83	P	8,48
(2) gef. (%):		58,96		10,91		3,69		8,39

Key: 1 Calculated (%)

2 Found (%)

Example 4

2-Hexadecylphosphocholine monohydrate

(Methylation of 3)

The procedure, workup, and purification can be carried out as in instruction 2.

Microanalysis (molecular weight 407.58)

(1) ber. (%):	C	59,27	H	11,37	N	3,29	P	7,28
(2) gef. (%):		59,14		11,11		3,14		7,09

Key: 1 Calculated (%)

2 Found (%)

Example 5

Oleylphosphomethyl ester, sodium salt monohydrate

(Phosphorylation, methanolysis, and LiBr cleavage)

The phosphorylation step takes place as in Example 1. For the methanolysis, the reaction mixture is mixed with methanol (10 mol; 320 g) and triethanolamine (1.8 mol; 180 g) at 20°C. The methanolysis is concluded after 30 min. Mixing with 1.5 L hexane and 1.5 L water is carried out, followed by a thorough shaking and removal of the solvent from the hexane phase. The oily residue is boiled with LiBr (2 mol; 174 g) in 1.5 L ethyl methyl ketone, under reflux. After 1 h, the reaction is complete. The solvent is removed, [the residue is] taken up in a mixture of 1 L methanol/water/chloroform; shaken thoroughly; and the lower chloroform phase, which contains the product, is isolated. For conversion into the sodium salt, the chloroform phase is treated with 1 L saturated NaCl solution. The chloroform phase is isolated and rotated on a rotary evaporator. The product is purified by chromatography on silica gel (see Example 2).

Microanalysis (molecular weight 402.50)

(1) ber. (%):	C 56,70	H 10,02	P 7,70
(2) gef. (%):	56,65	9,98	7,45

Key: 1 Calculated (%)

2 Found (%)

Example 6

Hexadecylphosphohexyl ester, sodium salt monohydrate

(Phosphorylation with phosphoroxychloride, phosphorylation with hexadecylphosphoric acid dichloride, methanolysis, cleavage with LiBr)

The phosphorylation of hexadecanol takes place as described under Example 1. The reaction mixture is directly reacted further with the dropwise addition of hexanol (1.5 mol, 303 g) and triethylamine (1.8 mol, 180 g) in 1.5 L THF. The temperature is now increased to 30°C. After 2 h, the reaction is ended. Methanolysis takes place as described in Example 5–likewise, the LiBr cleavage.

Microanalysis (molecular weight 446.59)

(1)	ber. (%):	C	59,17	H	10,83	P 6,94
(2)	gef. (%):		59,08		10,74	6,71

Key: 1 Calculated (%)

2 Found (%)

Example 7

Hexadecylphosphoglycol ester, sodium salt monohydrate

(Phosphorylation, ring closure with glycol, ring opening)

The phosphorylation takes place as described under Example 1. The reaction mixture is directly reacted further with the dropwise addition of ethylene glycol (1.5 mol, 93 g) and

triethanolamine (1.8 mol, 180 g) in 1.5 L THF. The temperature is increased to 60°C for the completion of the ring formation. After 2 h at this temperature, the reaction is concluded. The precipitated triethylamine hydrochloride is filtered via a porcelain frit and the filtrate is mixed, with vigorous stirring, at 20°C, with 1.5 L water. After 2 h, the hydrolysis is ended. The solvent is removed from the upper THF phase by rotating on a rotary evaporator, in a vacuum. The residue is mixed with a mixture of chloroform/methanol/semisaturated NaCl solution, shaken, and the phase separation is awaited. The lower chloroform phase contains the product. The solvent is removed and the product is purified by means of chromatography (Example 2).

Microanalysis (molecular weight 406.48)

(1) ber. (%):	C 53,19	H 9,92	P 7,62
(2) gef. (%):	53,07	9,73	7,53

Key: 1 Calculated (%):

2 Found (%):

The following glycol esters were produced in an analogous manner: tetradecyl phosphoglycol ester, octadecyl phosphoglycol ester, oleyl phosphoglycol ester.

Example 8

Hexadecylphosphohydroxyethylamide, sodium salt monohydrate

(Phosphorylation, ring closure with ethanolamine, ring opening with potassium carbonate in water)

The phosphorylation takes place as described under Example 1–likewise the ring closure. After removal of the triethylamine hydrochloride, the filtrate is mixed, with vigorous stirring, with 1 L 1M potassium carbonate solution in water. After 1 hour, the ring opening is concluded. In the upper THF phase, the solvent is removed, [the residue is] taken up in a mixture of 1 L chloroform/methanol/semisaturated NaCl solution; shaken thoroughly; and the chloroform phase is separated. After removal of the solvent, the product is chromatographed on silica gel and purified.

Microanalysis (molecular weight 405.50)

(1) ber. (%):	C	53,32	H	10,19	N	3,46	P 7,64
(2) gef. (%):		53,26		10,07		3,21	7,59

Key: 1 Calculated (%)

2 Found (%)

The following compounds were produced in an analogous manner: tetradecylhydroxyethylamide, octadecylhydroxyethylamide, oleylphosphohydroxyethylamide.

Example 9

Hexadecylphosphoglycerol, sodium salt [mono]hydrate

(Phosphorylation with phosphoroxychloride, phosphorylation with the phosphoric acid dichloride formed therefrom, methanolysis, LiBr cleavage, hydrolysis in 70% acetic acid)

The phosphorylation corresponds to Example 1. The reaction mixture is directly reacted further with the dropwise addition of 1,2-isopropylidene glycerol (1.5 mol, 198 g) and triethylamine (1.8 mol, 180 g) in 1.5 L THF. The temperature is increased to 30°C after the dropwise addition. The reaction is ended after 2 h. Methanolysis takes place according to Example 5–likewise the LiBR cleavage. The reaction product, sodium salt, is taken up in 2 L 70% acetic acid and heated to 60°C. The acetone formed is removed in a slight vacuum (water jet vacuum). The reaction is concluded after 2 h. Mixing with 2 L water is carried out, followed by extraction with 2 L chloroform. The chloroform phase is treated with 2 L 0.5 M sodium carbonate solution and separated after the phases separate. The solvent is removed and chromatography on silica gel is carried out.

Microanalysis (molecular weight 436.51)

(1) ber. (%):	C 52,28	H 9,70	P 7,10
(2) gef. (%):	52,13	9,59	6,91

Key: 1 Calculated (%)

2 Found (%)

The following compounds were produced in an analogous manner: tetradecylphosphoglycerol, octadecylphosphoglycerol, oleylphosphoglycerol.

Example 10

Hexadecylphosphoric acid-(N,N)-bis(chloroethyl)amide, Na salt [mono]hydrate (Phosphorylation with phosphoroxychloride, amide formation with bis(chloroethyl)amine, hydrolysis)

The phosphorylation step corresponds to Example 1. The reaction mixture is directly reacted further with the dropwise addition of bis(chloroethyl)amine in 1.0 L THF. Afterwards, triethylamine (0.4 mol, 40 g) in 0.5 L THF is added. After 3 h at 20°C, the reaction is ended. The precipitated triethylamine hydrochloride is separated via a porcelain frit, and the filtrate is mixed with vigorous stirring with 1 L 1M acetic acid for the hydrolysis. After 4 h, the upper THF phase is separated, freed from the solvent, and taken up in 1 L chloroform/methanol/0.5 M sodium carbonate. The chloroform phase is taken away; the solvent is removed; and the product is purified by chromatography on silica gel.

Microanalysis (molecular weight 486.452)

(1) ber. (%):	C	49,38	H	8,91	Cl	14,58	N	2,88	P	6,37
(2) gef. (%):		49,21		8,75		14,11		2,76		6,31

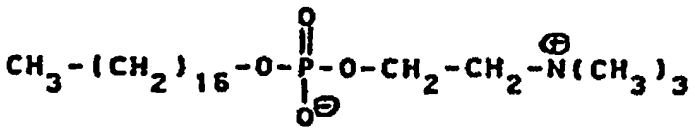
Key: 1 Calculated (%)

2 Found (%)

The following compounds were produced in an analogous manner: tetradecylphosphoric acid-(N,N)-bis(chloroethyl)amide, octadecylphosphoric acid-(N,N)-bis(chloroethyl)amide, oleylphosphoric acid-(N,N)-bis(chloroethyl)amide.

Example 11

Synthesis of heptadecylphosphocholine



25 g (0.097 mol) 1-heptadecanol and 16.7 g (0.166 mol) triethylamine are dissolved in 162 mL tetrahydrofuran and mixed with 16.9 g (0.11 mol) $POCl_3$ (phosphoroxytrichloride), dropwise, at 0°C. Stirring is carried out for 1 h at 0-10°C and after removal of the ice bath, a solution of 8.3 g (0.136 mol) ethanolamine and 16.7 g (0.166 mol) triethylamine is quickly added in drops (rise of temperature thereby, to approx. 55°C). After 1 h stirring at ca. 60°C, the precipitated triethylaminehydrochloride is suctioned off after cooling and washed with tetrahydrofuran. The filtrate is quickly stirred into 192 mL 2N HCl; the precipitated product is suctioned off; washed with water, and dissolved and recrystallized from methanol twice. It is then taken up in 290 mL methanol and mixed with a solution of 90 g K_2CO_3 in 82 mL water. At a maximum 30°C, a solution of 37.9 mL (0.4 mol) dimethyl sulfate in 48 mL methanol is slowly

dripped in. Stirring is carried out at 40°C for another hour, followed then by cooling to room temperature.

The precipitated product is suctioned off; washed with methanol; the filtrate is concentrated in a vacuum. The residue is purified by means of column chromatography. Melting point 254-256°C (decomposition).

Yield: 65 g.

Example 12

Synthesis of docosylphosphocholine

10.4 mL (0.115 mol) $POCl_3$ are dissolved in 600 mL ethanol and mixed with 32.6 g (0.1 mol) behenyl alcohol. With nitrogen and ice cooling, 23.7 mL (0.17 mol) triethylamine are added in drops [in such a way] that the temperature does not exceed 18°C. Subsequently, stirring is carried out for 2 h, with heating to room temperature. 9.16 g (0.15 mol) ethanolamine and 24.4 mL triethylamine (0.175 mL) are dissolved in dioxane and added in drops; a heating of the reaction mixture to 40°C occurs. The mixture is stirred for 1 hour at 60°C; it is filtered hot; and the solution is hydrolyzed with 200 mL 2N HCl. The precipitated product is suctioned off and washed with water.

Dissolving and recrystallizing from methynol is carried out twice.

Yield: 26.5 g Behenylphosphoethanolamine.

The product is converted into a paste in 250 mL methanol and mixed with 48.9 g (0.35 mol) K_2CO_3.

16.85 mL (0.177 mol) dimethyl sulfate are dissolved in 40 mL methanol and added in drops to the suspensions. (The temperature should not exceed 30°C thereby). After 2 h of stirring at 30°C, filtration over silica gel is carried out, followed by washing with methanol, and the filtrate is concentrated on a rotary evaporator.

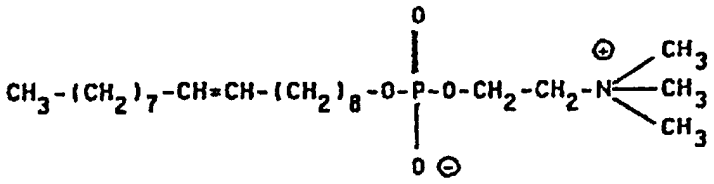
The residue is dissolved and recrystallized from methanol twice.

Melting point 61°C (decomposition).

Yield: 16.4 g.

Example 13

Synthesis of oleylphosphocholine



10.0 mL (0.11 mol) phosphoroxytrichloride ($POCl_3$) are dissolved in 50 mL absolute tetrahydrofuran and mixed, under ice cooling and in drops, with a mixture of 70 mL (0.5 mol) trimethylamine, 26.8 g (0.1 mol) oleyl alcohol, and 150 mL tetrahydrofuran. After 1 h, a solution of 8.5 mL (0.14 mol) ethanolamine and 20.9 mL (0.15 mol) triethylamine in 100 mL dioxane is carefully added in drops. The temperature of the reaction mixture rises to ca. 45°C. Boiling under

reflux is carried out for 1 hour; then, the precipitated triethylamine hydrochloride is suctioned off hot. The filtrate is mixed with 200 mL 2M hydrochloric acid and concentrated on a rotary evaporator. The filtrate is mixed with 200 mL 2M hydrochloric acid and concentrated on the rotary evaporator. The brown, oily residue is taken up in methanol and mixed with 83 g (0.6 mol) K_2CO_3. 37.8 g (0.3 mol) dimethyl sulfate in 40 mL methanol are added in drops to this suspension in such a way that the temperature does not exceed 30°C. Stirring is subsequently carried out after 2 h at room temperature, followed by cooling to 5°C, filtration over silica gel, and subsequent washing with methanol. The filtrate is concentrated on the rotary evaporator. The residue is chromatographed on silica gel.

Yield: 28 g white powder.

IR bands on KBr (wave number in cm^{-1})

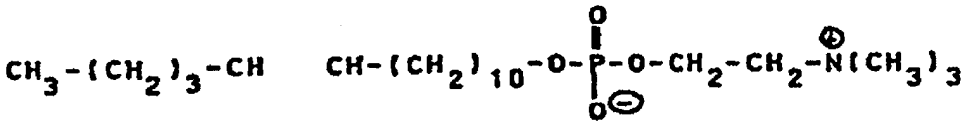
3415 (OH oscillation), 2920 (C-H oscillation)

2860 (C-H oscillation), 960 (P-O-C oscillation)

930 (P-O-C oscillation)

Example 14

Synthesis of hexadecenylphosphocholine



10.6 g (0.07 mol) $POCl_3$ are mixed, at -10°C and within 20 min, with a solution of 14.4 g (0.06 mol) cis11hexadecenol and 10.3 g (0.102 mol) triethylamine in 100 mL tetrahydrofuran. After 45 minutes at -10°C, 5.1 g (0.08 mol) ethanolamine and 10.6 g (0.105 mol) triethylamine–dissolved in 100 mL dioxane–are added in drops at room temperature. After 30 minutes, suctioning from the triethylamine hydrochloride is carried out. The filtrate is poured, while stirring, onto 2N HCl (120 mL) and concentrated on the rotary evaporator. The residue is taken up with 250 mL methanol and 33 g (0.24 mol) K_2CO_3 are added.

20.2 g (0.16 mol) dimethyl sulfate are dissolved in 125 mL methanol and added in drops so that the interior temperature does not exceed 40°C. The reaction is allowed to proceed for 2.5 h at 40°C, followed by cooling, filtering, and then the filtrate is concentrated on the rotary evaporator.

The substance is obtained as a light-brown resin and is present in the cis form.

Yield: 29 g.

IR bands on KBr (wave number in cm^{-1})

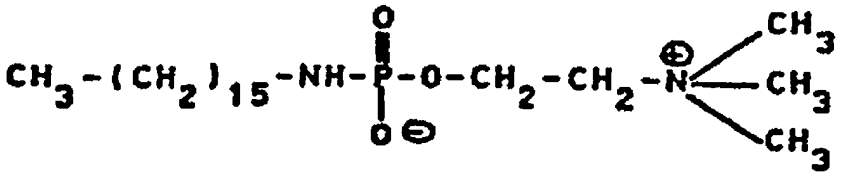
3415 (OH oscillation), 2925 (C-H oscillation)

2860 (C-H oscillation), 965 (P-O-C oscillation)

925 (P-O-C oscillation)

Example 15

Synthesis of hexadecylaminophosphocholine



7.05 mL (0.077 mol) phosphoroxytrichloride ($POCl_3$) and 50 mL tetrahydrofuran are mixed with a solution of 16.9 g (0.07 mol) cetylamine and 48 mL (0.35 mol) triethylamine in 150 mL tetrahydrofuran. After 1.5 h of stirring, a solution of 6.0 mL (0.1 mol) ethanolamine and 16.7 mL (0.12 mol) triethylamine in 100 mL dioxane is added in drops. After 1 h of heating under reflux, suctioning is carried out hot and the filtrate is mixed with 150 mL 2N HCl. The precipitate is suctioned off and dried; then dissolved in 150 mL methanol and mixed with 52.2 g (0.37 mol) K_2CO_3). 23.8 g (0.18 mol) dimethyl sulfate are added in drops so that the temperature does not exceed 30°C. Stirring is carried out for another 2 h at room temperature; then cooled, filtered over silica gel; and subsequently washed with methanol. The filtrate is concentrated on the rotary evaporator, and the residue is chromatographed on silica gel. The substance is a white, amorphous powder.

Yield: 14 g.

IR bands on KBr (wave number in cm^{-1})

3410 (OH oscillation), 2920 (C-H oscillation)

2855 (C-H oscillation), 980 (P-O-C oscillation),

940 (P-O-C oscillation)

Experimental report

Cytotoxic test of the compounds in accordance with the invention, on soft agar (agar gel with a small amount of agar)

100 L1210 cells are placed on cell culture plates in RPMI-1640 cell culture medium, which contains 10% fetal calf serum and 0.3% agar, and various concentrations of the substance to be tested.

The culture plates are incubated for 6 days under standard conditions (5% CO_2, 37°C, 95% relative humidity).

After incubation, the formed colonies of the L1210 cells are counted, and the results are expressed in % of the inhibition of the colony formation in comparison to a control without the test substance.

The EC_{90} values (the concentration, that produces a decline of colony formation by 90%) are graphically determined.

The results are summarized in the following table:

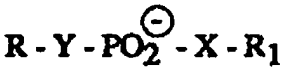
Compound	EC_{90} µg/ml	Orienting toxicity on mice LD 50 per os

D 19767	2.9	464 mg/kg
D 19867	10.0	732 mg/kg
D 2003	7.0	>1000 mg/kg

Claims

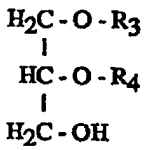
1. Drug characterized in that it

a) contains at least one compound of the following general formula:



or a physiologically acceptable salt hereof, wherein in formula I, R denotes a saturated or unsaturated hydrocarbon residue with 12 to 24 C atoms; X is an oxygen atom, NH, or NR_2; and Y, an oxygen atom or NH; R_1 is a C_1-C_8 alkyl group; or wherein R_1 represents a C_2-C_8 alkyl group, which is substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy; and R_2 is a C_1-C_8 alkyl group or a C_2-C_8 alkyl group, which is substituted with halogen; and

b) contains an alkyl glycerol of general formula II:



in which one of the residues R_3 and R_4 denotes an alkyl group with 3 to 12 C atoms; and the other residue, an H atom; and optionally other common pharmaceutical additives and diluents.

2. Drug, characterized in that it contains at least one compound of the following general formula:

I'

or a physiologically acceptable salt hereof, wherein in formula I', R denotes a saturated or unsaturated hydrocarbon residue with 12 to 24 C atoms; X is an oxygen atom, NH, or NR_2; and Y, an oxygen atom or NH; the residue R_1 represents a C_1-C_8 alkyl group, an unsaturated C_3-C_8 alkyl group, or a C_2-C_8 alkyl group, which is substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy; and R_2 represents a C_1-C_8 alkyl group or a C_2-C_8 alkyl group, which is substituted with halogen, optionally with additional common pharmaceutical additives and diluents.

3. Drug according to Claims 1 or 2, characterized in that R is an alkyl or alkenyl residue with 14 to 20 C atoms; X is an oxygen atom; and R_1 = trialkylammoniummethyl with 1 to 3 C atoms per alkyl group.

4. Agent according to one or more of the preceding claims, characterized in that it contains 5 to 200 mg compound in accordance with formula I or I' per mL alkyl glycerol for the topical treatment of skin tumors.

5. Agent according to one or more of the preceding claims, characterized in that it contains an alkyl glycerol mixture from nonyl or octyl glycerol, hexyl or pentyl glycerol, and propyl or ethyl glycerol and water.

6. Agent according to one or more of the preceding claims, characterized in that for the oral treatment of tumors, it is formulated as a beverage with a daily dosage between 5 and 100 mg/kg body weight.

7. Agent according to one or more of the preceding claims, characterized in that for the intravenous treatment of tumors, it contains a compound in accordance with general formula I or I' in a quantity of 5 to 100 mg/kg body weight in physiological saline solution.

8. Compounds of the following general formula:

I'

in which R denotes a saturated or unsaturated hydrocarbon residue with 12 to 24 C atoms; X is an oxygen atom, NH, or NR_2; and Y is an oxygen atom or NH; the residue R_1 represents a C_1-C_8 alkyl group, an unsaturated C_3-C_8 alkyl group, or a C_2-C_8 alkyl group, which is substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy; and R_2 represents a C_1-C_8 alkyl group or a C_2-C_8 alkyl group, which is substituted with halogen, and its physiologically acceptable salts, wherein such compounds where X and Y are both oxygen in formula I' are excepted.

9. Method for the production of compounds of the following formula: /

I

in which R denotes a saturated or unsaturated hydrocarbon residue with 12 to 24 C atoms; X is an oxygen atom, NH, or NR_2; and Y is an oxygen atom or NH; R_1 represents a C_1-C_8 alkyl group; or wherein R_1 represents a C_2-C_8 alkyl group, which is substituted with halogen, amino, C_1-C_6 alkylamino, hydroxy; and R_2 represents a C_1-C_8 alkyl group or a C_2-C_8 alkyl group, which is substituted with halogen, and its physiologically acceptable salts, characterized in that a compound of the following formula:

III

wherein R, R_1, Y, and X have the indicated meanings; Z is benzyl, C_1-C_6 alkyl, or C_2-C_6-alkenyl, can contain [in addition to] any hydroxy groups, amino groups, or C_1-C_6 alkylamino groups, a protecting group also; or two adjacent hydroxy groups can also be acetalized by an aliphatic C_3-C_6 ketone; is treated in an inert agent with alkali bromides, alkali iodides, lower alkyl magnesium halides, or amides; optionally, the protecting groups present in the compounds obtained are split off; optionally, the reaction products in which R_1 contains a halogen atom are reacted with ammonia or an amine of the formula $NR_5R_6R_7$, wherein the residues R_5, R_6, R_7 are the same or different and denote hydrogen or C_1-C_6 alkyl, and/or in the obtained products with an

amino group, this amino group is alkylated by C_1-C_6 alkyl groups; and the obtained products are optionally converted into salts.

10. Method for the production of compounds of formula I':

I'

in which R denotes saturated or unsaturated hydrocarbon residue with 12 to 24 C atoms; X is an oxygen atom, NH, or NR_2; and Y is an oxygen atom or NH; the residue R_1 represents a C_1-C_8 alkyl group, an unsaturated C_3-C_8 alkyl group, or a C_2-C_8 alkyl group, which is substituted with halogen, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, tri-C_1-C_6 alkylamino, hydroxy; and R_2 represents a C_1-C_8 alkyl group or a C_2-C_8 alkyl group, which is substituted with halogen, and its physiologically acceptable salts, wherein such compounds where X and Y are both oxygen in formula I' are excepted, according to the preceding method claim.

11. Method for the production of compounds of formula I according to one or more of the preceding method claims, characterized in that R is an unsaturated hydrocarbon residue with 12 to 14 C atoms; and Y, X, R_1, and R_2 have the indicated meanings; and wherein R can also be a saturated hydrocarbon residue with 12 to 14 C atoms, if X denotes the groups NH or NR_2, and Y is oxygen or NH.

12. Method for the production of an (antitumor-effective) synergistically effective drug, characterized in that 1 part by weight of at least one compound of formula I or I', wherein R, R_1, R_2, X, ad Y have the indicated meanings, and the compounds I and I' can also be present in the form of their physiologically acceptable salts, are mixed or homogenized with 1 to 30 parts by

weight of at least one glycerol ether of formula II, wherein R_3 and R_4 have the indicated meanings, or a mixture of such glycerol ethers and optionally 1 to 30 parts by weight water and optionally other common carrier substances and/or diluents or auxiliary substances, at temperatures between 20 and 120°C, and optionally the thus obtained mixture for the production of preparations, which in the dosage unit, contain 5 to 2000 mg active substance of formula I or I', are poured into hollow cells of an appropriate size or poured into capsules of an appropriate size or are granulated and then optionally are pressed into tablets, with the addition of other common auxiliaries.

13. Method for the production of an (antitumor-effective) synergistically acting drug, characterized in that 1 part by weight of at least one compound of formula I or I', wherein R, R_1, R_2, X, and Y, have the indicated meanings, and the compounds I and I'
can also be present in the form of their physiologically acceptable salts, are mixed or homogenized with 1 to 30 parts by weight of at least one glycerol ether of formula II, wherein R_3 and R_4 have the indicated meanings, or a mixture of such glycerol ethers and optionally 1 to 30 parts by weight water and one or more of the following salts: starch, cellulose, lactose, formalin-casein, modified starch, magnesium stearate, calcium hydrogen phosphate, highly disperse silica, talc, phenoxyethanol; the mixture obtained is granulated, optionally with an aqueous solution, which contains, as a component, at least gelatin, starch, polyvinylpyrrolidone, vinylpyrrolidone-vinyl acetate copolymer, and/or polyoxyethyl sorbitan monooleate; the granulate is homogenized, optionally with one or more of the aforementioned auxiliaries; and this mixture is pressed into tablets, or poured into capsules, wherein in the dosage unit, such tablets or capsules contain 5 to 2000 mg active substance of formula I.

14. Method for the production of an (antitumor-effective) synergistically acting drug, characterized in that 1 part by weight of at least one compound of formula I or I', where R, R_1, R_2, X, and Y have the indicated meanings, and the compounds I and I' can also be present in the form of their physiologically acceptable salts, are suspended in melted hard fat and homogenized with 1 to 30 parts by weight of at least one glycerol ether of formula II, wherein R_3 and R_4 have the indicated meanings, or a mixture of such glycerol ethers and optionally 1 to 30 parts by weight water, after the addition of soya lecithin and optionally 0.1-0.5 part by weight phenoxyethanol (with reference to 1 part by weight compound I or I')'; and subsequently, the mixture is poured out into hollow cells, wherein the dosage unit contains 5 to 2000 mg active substance of formula I.

15. Method for the production of an (antitumor-effective) synergistically active drug (salts, cream, emulsion), characterized in that 1 part by weight of at least one compound of formula I or I', where R, R_1, R_2, X, and Y have the indicated meanings, and the compounds I and I' can also be present in the form of their physiologically acceptable salts, are homogenized with 1 to 30 parts by weight of at least one glycerol ether of formula II, wherein R_3 and R_4 have the indicated meanings, or a mixture of such glycerol ethers and optionally 1 to 30 parts by weight water, at a temperature between 50 to 120°C, optionally in the presence of one or more emulsifiers and/or 0.1 to 0.5 part by weight phenoxyethanol (with reference to 1 part by weight compound I or I') with at least one of the following substances: paraffin, Vaseline, aliphatic alcohol with 12 to 25 C atoms, sorbitan monopalmitate, aliphatic monocarboxylic acid with 15 to 20 C atoms, polyoxyethylene polyol fatty acid ester; and are optionally emulsified with the addition of a multivalent lower aliphatic alcohol.

16. Method for the production of an (antitumor-effective) synergistically acting solution, characterized in that 1 part by weight of at least one compound of formula I or I', wherein R, R_1, R_2, X, and Y have the indicated meanings and the compounds I and I' can also be present in the form of their physiologically acceptable salts, are dissolved with 1 to 30 parts by weight of at least one glycerol ether of formula II, wherein R_3 and R_4 have the indicated meanings, or a mixture of such glycerol ethers and optionally 1 to 30 parts by weight water, at a temperature between 30 to 100°C, optionally in the presence of 0.1 to 0.5 part by weight phenoxyethanol (with reference to 1 part by weight compound I or I') and optionally in the presence of an emulsifier, and the solution thus obtained is optionally filled with enough water or vegetable oil that the end solution contains 0.1 to 5 wt% active substance of formula I or I'.

17. Method for the production of hexadecyl, tetradecyl, octadecyl, eicosyl, dodecyl, oleyl, and cis-11-hexadecenyl-phosphoethanolamine and the corresponding cholines, characterized in that phosphoroxychloride is first reacted with hexadecanol, tetradecanol, octadecanol, eicosanol, dodecanol, octadecen-(9c)-ol or cis-11-hexadecanol-(1); the reaction mixture is then reacted with ethanolamine; and the reaction product is treated with formic acid, and optionally the products obtained are methylated to the corresponding cholines.

18. Method for the production of compounds of the following formula:

R-O-PO(OH)-O-CH_2-CH_2-OH

wherein R is hexadecyl, tetradecyl, octadecyl, or oleyl, characterized in that phosphoroxychloride is first reacted with hexadecanol, tetradecanol, octadecanol, or octadecen-(9c)-ol; then the reaction mixture is reacted with ethylene glycol; the reaction product is treated with water, and optionally, the compounds obtained are converted into salts.

19. Method for the production of compounds of the following formula:

R-O-PO(OH)-O-$NHCH_2$-CH_2-OH

wherein R is hexadecyl, tetradecyl, octadecyl, or oleyl, characterized in that phosphoroxychloride is first reacted with hexadecanol, tetradecanol, octadecanol, or octadecen-(c)-ol; then, the reaction mixture is reacted with ethylene glycol; and the reaction product is treated with potassium carbonate; and optionally, the compounds obtained are converted into salts.